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AD833622

TRANSLATION NO. 1761

~~DDOCCG~~ CA-18-064-D5-00039(A)

DATE: 23 May 1966

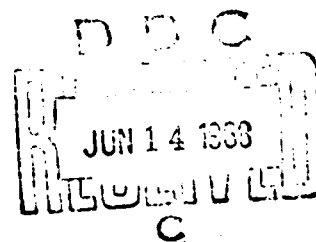
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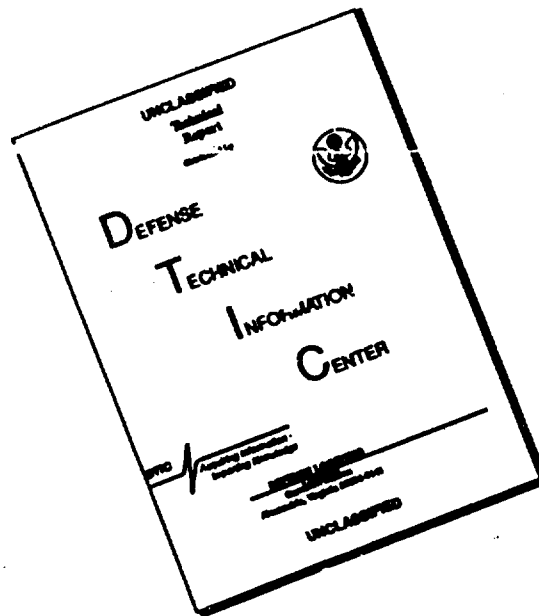
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CA-18-064-D5-00039(A)

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23 May 1966

RETICULOCYTOSIS IN RATS AFFECTED WITH ANTHRAX

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RETICULOCYTOSIS IN RATS AFFECTED WITH ANTHRAX

[Following is a translation of an article by Lucio Severini in the Italian-language Boll. Soc. Ital. Biol. Sper. (Bulletin of the Italian Society for Experimental Biology), Vol 9, 1934, pages 848-851.]

In another paper (Boll. Soc. Ital. Biol. Sper. Vol 9, 1934, pages 551 and 555) I reported on the behavior of the granulo-filamentose substance in both intact and splenectomized rats.

This research showed that the increase in the number of reticulocytes (reticulocytosis) is constant in splenectomized rats, independent of whether Bartonella is present; those rats having Bartonella present but with no appearance of anemia, do not show any change in their red blood cells and the granulo-filamentose substance remains unchanged.

These facts can be interpreted in two ways: I. The increase in reticulocytes in the splenectomized rats was related to blood regenerative phenomena secondary to the destruction of part of the red blood cells; II. Or, admitting with the majority that Bartonella have a bacterial nature (with certain reservations for some forms of Bartonella; see B. de Vecchi, Athena, 1933, Vol 104, pages 2113-2115), the state of septicemia, itself, would be responsible for stimulating the marrow and inducing the reticulocytosis.

In other words, the question comes up as to whether reticulocytosis in splenectomized rats is infectious or not.

A comparison between the behavior of reticulocytosis in cases of Bartonellosis with that of reticulocytosis in experimentally induced septicemia in rats seemed to me to be able to offer as a matter of course in a certain sense

some clues to support or disprove the idea that Bartonellosis was infectious in nature.

So far as I was able to determine, the granulo-filamentous substance has been studied in human subjects only in cases of sepsis, by J. Kiroly (Presse Med., 1933, Vol 104, pages 2113-2115) who investigated the quantitative and qualitative changes in the reticulocytes in puerperal sepsis and in acute peritonitis during the course of abscesses and phlegmons. The coarse or large-granulated reticulocytes are attributable, according to J. Kiroly, to septic anemia as long as the hematopoietic system is in a condition capable of reacting; when this capacity begins to fail, that is, 24 to 48 hours before death, the older forms with delicate granules would be held to predominate.

So far as I could find out, no investigator had ever studied the changes in the granulo-filamentous substance in experimentally induced septicemia.

For the present experiments I used white rats coming from the same Turin batch as those used by me in the preceding research.

The microorganism used to induce the septicemia was *Bacillus anthracis*, injected by the intraperitoneal route in the amount of 1/10 of a ml. of a 24-hr. broth culture medium. I injected 12 white rats which died about 80 hrs. later due to septicemia (blood culture tested for *Bacillus anthracis* showed positive).

Before giving the injection I carried out a morphological examination of the blood and brought out the granulo-filamentous substance visibly by using Brilliant Cresil Blue using the technique of W. Ederle (Klin. Woch., 1933, 13.); comparison with the findings obtained by me in the previous report showed that the data obtained agreed completely with the norm.

On having injected the microbes into the rats I repeated the morphological examination of the blood and I studied the granulo-filamentous substance at different stages.

This research showed: 1) Considerable, constant anemia (4,100,000-5,700,000); 2) Considerable increase in the overall number of reticulocytes (29-35 per cent) and 3) Peculiar qualitative changes in the reticulocytes, that is, a decrease in the number of forms having large-granule, granulo-filamentous substance and a corresponding increase in the number of forms having a delicate-structured granulo-filamentous substance. This picture begins to take shape even

after only 15 hours from the time of inoculation. [Note: By way of definition, the coarse or large-granule type granulo-filamentous substance is clustered together in clods so close to one another that most of the red cell remains covered or there is a single, and rarely a double, roughly defined bar that covers about one third of the cell. The delicately-structured granular forms, already spoken of as "having delicate granulations" in previous papers, have, here, in these experiments on septicemia, a new aspect which nevertheless is fully classifiable as the delicate-granulo-filamentous substance took on the form of a densely packed, fine powder or dust; a brief examination could lead one to erroneously classify these forms among the types having large granulations while, in fact, the structures involved are extremely delicate, even though crowded together. This morphological type, of a special kind, is not found in normal rats but is undoubtedly an aspect of the basic type "with delicate granulations."]

In any case, the anemia appearing in the rats affected by carbuncular septicemia is continuous, but not at all at a high level; this is clearly shown by a morphological examination of the blood. In view of the nature of the findings and based on information obtained in other experimentally induced and spontaneous infections, I would be inclined to see a direct relationship between the ruemia and the sepsis.

Interpretation of the reticulocytosis is a more difficult matter. From a general standpoint the reticulocytosis can be interpreted in various ways. 1) Independent of any toxic-infectious causes, the marrow of the bones responds to the removal or destruction of a certain number of red cells by automatically dumping into the blood stream a corresponding number of young red blood cells, rich in granulo-filamentous substance (reticulocytosis unrelated to any sepsis). 2) The toxic infections can, however, by stimulating the bone marrow, directly induce reticulocytosis (Kiroly), a phenomenon of functional irritation which can be followed by serious alterations going as far as myelophthisis. 3) It will readily be discernible that toxic infections, stimulating the marrow and at the same time producing a certain destruction of red blood cells by means of hemolysin, can induce reticulocytosis based on both mechanisms mentioned above.

In the experiments reported by me, due to the fact that the reticulocytosis is much more intense than that which ordinarily accompanies anemia, it seems to me to be justifiable to consider the prospect that the carbuncular infection

Table

Changes in reticulocytes of rats with septicemia
due to *Bacillus anthracis*, 78 hours
after inoculation

⑤ Rat N.	④ Global count	③ Reticulocyte + granulated granules		① Reticulocyte + granulated definite		② Total %
		⑥ Granulated granules + late	⑦ Granulated granules + dense	⑧ Granulated + trace reticuli	⑨ Granulated rare	
1	4,100,000	10	3	27	60	31
2	4,700,000	12	1	5	82	20
3	3,000,000	7	—	60	24	30
4	3,300,000	12	2	17	60	35
5	4,900,000	14	4	21	61	20
6	3,700,000	9	1	25	25	31
7	4,100,000	11	3	31	25	27
8	4,300,000	14	2	45	45	20
9	3,100,000	10	15	20	25	25
10	4,500,000	9	6	9	70	32
11	3,000,000	11	9	20	20	22
12	3,200,000	10	2	10	70	31

[Legend]: a) Rat No.; b) Red cells; c) Large or coarse granulated reticulocytes; d) Coarse, crowded together granulations; e) Granulations arranged in bars; f) Delicately-granulated reticulocytes; g) Filaments with tenuous reticulum; h) Scarce granulations; i) Total percent.

induces at the same time a certain destruction of red blood cells and that it also directly stimulates the bone marrow; I consider this interpretation only provisionally in view of the absence of hematological research in the field of carbuncular infection and the need for other investigations in the experiments being carried out by me.

Taking up now the qualitative changes in the granulofilamentous substance, the considerable decrease in reticulocytes having large granulations (groups I and II) signifies a shortage of young reticulocytes in the circulation. Correspondingly, the high percentage of delicately-structured reticulocytes (groups III and IV) indicates an abundance of mature reticulocytes.

The interpretation proposed by J. Kiroly does not seem convincing to me, that is, that the disappearance of young reticulocytes in cases of sepsis is related to a decrease in the regenerative potential of the bone marrow. If such were true, then changes of this kind would apparently

have to be accompanied by some quantitative decrease in red blood cells with granulo-filamentous substance; but such a parallel set of conditions does not exist so the disappearance or decrease in young reticulocytes probably takes place because the organism attempts to speed up the maturation of some reticulocytes in order to compensate for the decrease in number of red cells.

If we return at this point to the problem of Bartonellosis, and the interpretation of reticulocytosis present, ~~in it, we can~~ note that the reticulocyte picture in Bartonellosis differs from that found in carbuncular sepsis, with delicately-granulated forms predominating in the latter and large or coarse granulations predominating in the former. ~~This means~~ that the reticulocytosis present in splenectomized anemia is of the less mature type while that present in carbuncular sepsis is of the more mature type.

Bartonelle's anemia, then, does not fit in completely with the infectious anemias, at least with respect to the reticulocytes.

Perugia University Institute of Pathological Anatomy.

Paper read at the Florence Section Meeting, 6 July 1934.

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